REMARKS

The previous objection to the specification for containing an embedded hyperlink, the previous objection to claim 1, and the previous rejection of claims 1 – 7 and 10 – 17 have been withdrawn. Claims 1, 11, 15, 17 and 32 – 38 are pending, and the subject of the present examination; claims 8 9, and 18 – 31 stand withdrawn and are currently cancelled.

Rejections Under 35 U.S.C. §§ 101, and 112, First Paragraph

Claims 1, 11, 15 and 17 stand rejected, and new claims 32 – 38 are rejected, under 35 U.S.C. § 101 as the invention allegedly is not supported by either a specific and substantial asserted utility or a well-established utility, for the reasons set forth in the previous Office Action. In the present Office Action, the Examiner asserts that Applicant has not shown which of the diseases listed in the specification are associated with the claimed nucleic acid. The Examiner then goes on to assert that the Dale and Nicklin reference previously submitted only teaches the placement and orientation of several IL-1 receptor family members on chromosome 2 and asserts that these might be useful as a resource for sequencing and identification of polymorphic markers.

With respect to single nucleotide polymorphisms (SNPs), the Examiner alleges that while there is a large body of knowledge related to such polymorphisms in general, the art is highly unpredictable with regard to the functionality of polymorphic sites. In support of this proposition, the Examiner cites Hacker et al., as being unable to confirm an association between a gene polymorphism and ulcerative colitis, and Pennisi et al. for allegedly teaching that it is difficult to associate SNPs with disease states or to even identify key genes as being associated with disease. The Examiner further asserts that, in the absence of a credible utility, one of ordinary skill in the art would not know how to use the claimed invention, and thus sets forth a corresponding rejection under 35 U.S.C. § 112, first paragraph. Applicant respectfully disagrees with both aspects of the rejection for the reasons set forth below.

The U.S. Court of Appeals for the Federal Circuit has stated: "An invention need not be the best or the only way to accomplish a certain result, and it need only be useful to some extent and in certain applications." *Carl Zeiss Stiftung v. Renishaw plc*, 20 U.S.P.Q.2d 1094, 1100 (1991). Therefore, Applicant's claimed nucleic acids do not need to be the best or only way to identify human chromosome 2, to analyze abnormalities associated with genes mapping to chromosome 2, to distinguish conditions in which this marker is rearranged or deleted, or to serve as a positional marker to map other genes of unknown location. Rather, the claimed nucleic acids need only be useful to some extent and in certain applications. Applicant's claimed nucleic acids fulfill this requirement.

The present claims recite isolated nucleic acids comprising SEQ ID NO:3 and isolated oligonucleotides having at least 17 or at least 30 contiguous nucleotides of SEQ ID NO:3, as well as nucleic acids encompassing alleles associated with specified nucleotides (i.e., polymorphisms). Applicant asserts a specific utility for these nucleic acids, namely, that all or a portion of the claimed nucleic acids of SEQ ID NO:3, including fragments (i.e., oligonucleotides), can be used by one skilled

in the art using well-known techniques to analyze abnormalities associated with genes mapping to chromosome 2. This enables one to distinguish conditions in which this marker is rearranged or deleted. (Specification at 30, lines 26-29). Oligonucleotides that encompass any of the alleles associated with nucleotides 151-153 and/or nucleotides 130-132 are useful for detecting FIL-1 theta polymorphisms. These are credible "real world" utilities that can be practiced with Applicant's invention without any need for additional research into the utility of FIL-1 theta.

Applicant is not proposing that the claimed nucleic acids be used to determine whether genetic abnormalities exist, or whether polymorphisms exist. Such uses might be considered a use in research to identify a utility. This distinction is discussed in the analysis of the law governing the utility requirement to support the Utility Guidelines issued by the Office, the relevant portion of which states:

> Some confusion can result when one attempts to label certain types of inventions as not being capable of having a specific utility based on the setting in which the invention is to be used. Inventions that are to be used exclusively in a research setting (i.e., "research tools") illustrate the problem. Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the specific invention is in fact "useful" in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified utility and inventions whose utility requires further research to identify or reasonably confirm. Labels such as "research tool," "intermediate" or "for research purposes" are not helpful in determining if an applicant has identified a specific utility for the invention. (**Utility Examination Guidelines,** Docket No. 950706172-5172-01)

Thus, the mere fact that one of ordinary skill in the art could use the claimed inventive nucleic acids in a research setting to detect genetic abnormalities or the presence of specific polymorphisms is not dispositive of a lack of "real world" utility.

As objective evidence of the "real world" utility of Applicant's nucleic acids, Applicant submits herewith Exhibits 1-6, which demonstrate that the skilled artisan could use Applicant's claimed invention for the detection of chromosome 2 and for the detection of rearrangements associated with chromosome 2.

Giardino et al. (Exhibit 1) analyzed a chromosomal rearrangement in a patient with psychotic illness and mild mental retardation. Giardino et al., at 319, col. 2, last full paragraph. Fluorescence *in situ* hybridization (FISH) was used to characterize a small supernumerary marker chromosome (SMC) found in the cells of the mother and child. *Id.* at 321, Fig 2. Giardino et al. determined that the SMC was derived from the proximal region of human chromosome 2. *Id.* at 321, Table 1. Several probes for 2q11.2 and 2q12 detected both the normal chromosomes and the SMC, whereas more distal probes for 2q12 detected only the normal chromosomes. *Id.*

Riegel et al. (Exhibit 2) examined a patient with various abnormalities, and found an abnormal chromosome 2. Riegel et al. at 76, Abstract. Using FISH, they determined that there was a

direct tandem duplication of 2q11-q13.2. *Id.* Several probes for 2q11.1-q13 detected a single signal on one chromosome and two signals on the abnormal chromosome. *Id.* at 78, Table 1. In contrast, a probe for 2q14 detected a single signal on both chromosomes. *Id.* Wang et al. (Exhibit 3) examined a fetus with various abnormalities, and found an abnormal chromosome 2. Wang et al. at 312, Abstract. Using FISH, they determined that there was a triplication of 2q11.2-q21. *Id.*

Glass et al. (Exhibit 4) examined a patient with various abnormalities, and found an abnormal chromosome 2. Glass et al. at 319, Abstract. Using FISH, they determined that there was a proximal 2q trisomy (2q11.2-q21.1). *Id.* FISH showed an insertion of chromosome 2-derived material into the middle of the short arm of chromosome 8. *Id.* at 320, Figure 4. Moreover, in Table 2, Giardino et al. (Exhibit 1) provide a list of chromosome 2 partial trisomy cases and associated phenotypic findings. All of the trisomy cases appear to be associated with the proximal region of chromosome 2, which is the region to which Applicant mapped IL-1 theta DNA.

Mu et al. (Exhibit 5) examined a patient with various abnormalities, and found an abnormal chromosome 2. Mu et al. at 57, Summary. They determined that there was a tandem duplication of 2q11.2-q14.2. *Id.* *Id.* at 78, Table 1. Although Mu et al. did not perform hybridization analyses, probes mapping to the proximal region of chromosome 2 would have been useful for determining the presence of normal chromosome 2 sequences on one of the chromosomes and for characterizing the duplicated region of the abnormal chromosome.

Reddy et al. (Exhibit 6) studied intrachromosomal triplications, including a triplication of 2q11.2-2q21. Reddy et al. at 134, Abstract. Reddy et al. states: "Triplications can be mistaken for duplications. Therefore, in assessing duplications, FISH confirmation is recommended." *Id.* Consequently, it is appreciated in the art that FISH is useful for assessing duplications and confirming triplications, including those involving the proximal region of chromosome 2.

Thus, probes mapping to the proximal region of chromosome 2 are useful for determining the presence of normal chromosome 2 sequences and for characterizing the composition of the SMC described by Giardino et al. Such probes are also useful for determining the presence of normal chromosome 2 sequences and for characterizing the duplicated region of chromosome 2 described by Riegel et al. and Mu et al. and the triplication described by Wang et al. The usefulness of probes from the proximal region of chromosome 2 in assessing duplications and confirming triplications is shown by Reddy et al. Moreover, probes mapping to the proximal region of chromosome 2 are also useful for detecting and analyzing proximal 2q trisomy as described by Glass et al. (and summarized by Giardino et al.).

Since Applicant's nucleic acid localizes to the proximal region of chromosome 2, it is useful as a probe for detecting the abnormalities discussed above. Furthermore, as stated in Giardino et al., "FISH analyses using unique sequences are useful means of obtaining information about the euchromatic regions contained in an SMC and delineating new chromosomal syndromes, aimed to

offer suitable genetic counseling, especially when an SMC is observed in prenatal diagnosis." Giardino et al. at 322, col. 2, first ¶. Applicant submits that such uses are "real world" uses.

With respect to the utility of the clamed invention in detecting polymorphisms of FIL-1 theta, the Examiner cites Hacker et al., as being unable to confirm an association between a gene polymorphism and ulcerative colitis, and Pennisi for allegedly teaching that it is difficult to associate SNPs with disease states or to even identify key genes as being associated with disease. Applicant notes that Hacker et al. were not able to confirm the association of polymorphism with disease in the population they were studying, and in fact state on page 625, final paragraph, column 2, that their finding raises the question of whether such association may be found only in certain ethnic groups.

Moreover, Pennisi in her introductory comments state:

> Although no one doubts that SNPs will ultimately prove to have some value in tracking disease genes and understanding human diversity, new results ... suggest that the task could prove more difficult that many had initially thought.
> Pennisi E., page 1878, column 1, second paragraph.

She concludes by quoting one of the contributors to the article as noting that as long as SNPs are not regarded as a panacea, there is value in producing them, and that they will make a difference.

Thus, rather than suggesting that SNPs do not have a real-world use, the articles cited by the Examiner actually teach that those of skill in the art recognize that SNPs are useful, at the very least in a research setting for investigating the correlation of genetic profiles and disease. This view is confirmed in three more recent review articles submitted herewith as Exhibits 7, 8 and 9 (Shastry, Brazell et al. and Roses, respectively.).

Shastry briefly describes the efforts being made by several organization to generate a high density SNP map of the human genome (page 562, column 1), and discusses the use of such maps in evolutionary biology, gene discovery and mapping, prediction of drug and environmental response, diagnostic tests, heterogeneity testing and association studies (page 563, column 1). Shastry concludes that despite the complexities involved in such studies, finding out how SNPs affect an individual's health and correlating specific SNPs with disease will revolutionize the treatment of most killer diseases (page 564, column 2).

Brazell et al. discuss the application of pharmacogenetics in increasing the safety and efficacy of medicines. On page 225, at column 2, they also discuss the effort to prepare a SNP map of the human genome, and note that the frequency, stability and even distribution of SNPs make them valuable genetic markers. Brazell et al. discuss the proof of principle study that used SNP mapping to locate the APOE Alzheimer's disease susceptibility gene, and note that SNP technology has been used to narrow the search for other susceptibility genes (page 226, column 1). They conclude that pharmacogenetic technology offers significant opportunity to improve the discovery, development and delivery of medicines.

Roses also summarizes the usefulness of SNPs and a SNP map of the human genome in the pharmaceutical industry. On page 542, final paragraph of column 1, he notes that the ability to identify and study susceptibility genes for common diseases has expanded, and further that by using high-density SNP mapping as a tool, it is feasible to study multiple genetic factors simultaneously. From reading Roses it is clear that knowledge of the existence, and location, of SNPs provides a public benefit in enhancing the SNP map of the human genome. Even if such knowledge is derived in a research setting, the tools used in its derivation are clearly 'useful' in accordance with patent law and thus meet the utility requirements of 35 U.S.C. § 101.

Exhibits 1-9 provide evidence that, as Applicant asserted in the specification, the claimed nucleic acids can be used to identify human chromosome 2, to distinguish conditions in which this marker is rearranged or deleted, and/or to detect polymorphisms of FIL-1 theta, all of which are real-world, substantial and credible utilities. In view of this evidence, Applicant submits that the claimed nucleic acids are useful at least "to some extent and in certain applications," which is sufficient to fulfill the utility requirement of 35 U.S.C. § 101. *See Carl Zeiss Stiftung v. Renishaw plc*, 20 U.S.P.Q.2d 1094, at 1100. Moreover, the aforementioned utilities are substantial: they define a real world context of use and provide a clear public benefit. The Exhibits also demonstrate that the asserted utilities are credible; they are neither inconsistent with known scientific principles, nor speculative. Accordingly, the claimed invention is supported by at least one specific and substantial (and well-known) utility; Applicant requests that the rejection under 35 U.S.C. § 101 be withdrawn.

Moreover, inasmuch as the claimed invention posses utility, one of ordinary skill in the art would know how to make and use it in light of the disclosure, as discussed above; Applicant requests that the rejection under 35 U.S.C. § 112 also be withdrawn.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 32 – 38 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite in reciting " ... encompassing an allele at amino acid 44, ... encompassing an allele at amino acid 51, ..." According to the Examiner, it is unclear whether the DNA of SEQ ID NO:3 encompasses an allelic variant that encodes a threonine or isoleucine at amino acid 44, an allelic variant that encodes aspartic acid or alanine at amino acid 51 of the encoded polypeptide, or whether SEQ ID NO:3 itself comprises either a threonine or isoleucine at amino acid 44 and aspartic acid or alanine at amino acid 51. Claims 33 and 37 through 38 were rejected as depending on the allegedly indefinite claims.

Applicant respectfully submits that one of ordinary skill in the art would understand a reference to a particular amino acid being present at an allele to mean that the amino acid is present in the encoded polypeptide. Nonetheless, in an effort to be cooperative and speed allowance of the claims, claims 32 through 37 have been amended as shown in the listing of the claims. Applicant believes that the amendments address the rejection under 35 U.S.C. § 112, second paragraph, and accordingly request that it be withdrawn.

CONCLUSIONS

Claims 1, 11, 15, 17 and 32 through 38 are currently under consideration in the application and stand rejected under 35 U.S.C. §§ 101, 112, first and second paragraphs. It is believed that these grounds for rejection have been overcome by virtue of the amendments and comments set forth above. Accordingly, the Applicant believes that the claims are in condition for allowance and notification to that effect is respectfully requested. If further issues remain in this application, the examiner is asked to contact the undersigned at her direct dial number given below.

Respectfully submitted,

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